

EFFECT OF POLY(ETHYLENE GLYCOL) (PEG) ON THE STABILITY AND OPENING VELOCITY OF THERMOSENSITIVE LIPOSOMES

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Introduction

To investigate the role of Poly(ethylene glycol) (PEG) as possible mediators of heat induced drug release in thermosensitive liposomes (TSL), liposomes based on the classical formulation DPPC/DSPC 8:2 (m/m) with increasing concentration of DSPE-PEG2000 (1 to 20%) have been prepared and compared with regard to stability, content release and kinetics. Moreover, the influence of membrane incorporated 1-palmitoyl-2-hydroxy-*sn*-glycero-3-phosphocholine (MPPC) and hexadecylphosphocholine (HePC) into PEGylated TSL was studied and compared to our long-circulating formulation DPPC/DSPC/DPPGOG 5:2:3 (m/m) (Clin Cancer Res. 2004).

Methods

Liposomes were prepared by the lipid film hydration and extrusion method. The size and ζ -potential was determined by Photon Correlation Spectroscopy and T_m was determined by Differential Scanning Calorimetry. The encapsulated fluorescence dye carboxyfluorescein (CF) was used to monitor potential drug release at chosen temperatures or drug leakage over a given period of time.

Results

All tested formulations showed a remarkable storage stability over months. The leakage of CF was below 4% when stored at 4°C. DSPE-PEG2000 had only a minor effect on the temperature dependent-content release. While the difference between T_m was negligible, the total content release at 42°C varied between 45 and 60%. When looking at the in vitro stability at 37°C in fetal serum albumin, the PEGylated liposomes became unstable after 6 hours, while the DPPGOG-containing long circulating formulation was stable up to 12 hours. By adding 5% MPPC or HePC the total content release and opening velocity could be dramatically increased, yielding to an burst release when using MPPC. Nevertheless, this addition had negative effects on the in vitro stability. Those formulations released 60% of CF during 8 hours of incubation. Preincubation of tested TSL at 37°C increased the content release at 42°C significantly. This time-dependent effect may be a result of the interaction with serum components like the protein albumin. The influence of albumin was assayed and we found a clear concentration dependency. When using 10% DSPE-PEG2000 in the TSL, the overall content release rate increased from 10 to 30%, when increasing the concentration of human serum albumin from zero to 20%.

Conclusion

The choice of the right lipid composition for TSL is important for their success in the therapy of solid cancer in combination with hyperthermia. The tested formulations showed great differences in regard to stability and opening velocity. In addition to it, our data indicate the importance of the time interval between i.v. application of TSL and hyperthermic treatment.